REMARKS

Claims 86-98 and 100-102 are pending in the application. Claim 90 remains withdrawn.

Applicants wish to thank the Examiner for his time and consideration in the telephone interview with Applicants' representatives Louis Myers and Allyson Hatton on October 8, 2008, and also for his and Examiner Robert Wax's time and consideration during the telephone interview with Louis Myers and Allyson Hatton, and Lisa Geller, from Biogen Idec, on October 15, 2008. The outstanding obviousness rejection was discussed during both conferences, and no agreement was reached during either of the two interviews. The below remarks are to summarize the points made during the interviews.

Attached is a Supplemental Information Disclosure Statement (IDS). Applicants respectfully requested that the Examiner consider the reference cited on the IDS and indicate that he has done so by initialing and returning the form PTO/SB/08(a).

35 U.S.C. § 103

Claims 86-89, 91-98, and 100-102 stand rejected under U.S. Patent No. 6,692,742 ("the '742 patent") in view of Lokhorst *et al.*, *Blood* 84:2269-2277, 1994 ("Lokhorst") and Masellis-Smith *et al.*, *Cancer Res.* 57:930-936, 1997 ("Masellis-Smith"). Applicants respectfully traverse the rejection.

Applicants understand the rejection to be based on the following reasoning. The '742 patent is relied on for at least describing a combination of melphalen and an anti-IL-6 receptor antibody for treatment of multiple myeloma (MM). Lokhorst *et al.* is relied on for at least teaching that anti-VLA-4 antibodies inhibited binding of purified myeloma cells to long term bone marrow cultures (LTBMC) from patients with multiple myeloma and that the antibodies inhibited IL-6 secretion by the LTBMC cells. Masellis-Smith *et al.* is relied on for at least teaching that anti-VLA-4 antibodies inhibited $CD19^+$ multiple myeloma blood B cell interactions with bone marrow fibroblasts *in vitro*. From this the PTO concluded that it would have been obvious to substitute the anti-IL-6 receptor antibodies taught by the '742 patent with the anti-VLA-4 antibodies taught by Lokhorst *et al.* or Masellis-Smith *et al.* in a method of treating multiple myeloma. The PTO further argued that one of ordinary skill in the art would have been

motivated to substitute the anti-IL-6 receptor antibody with the anti-VLA-4 antibody, because antibodies against alpha4 integrin inhibit cell-cell contact which is a prerequisite for IL-6 induction as taught by Lokhorst *et al.*

Applicants disagree with the conclusions of the Unites States Patent and Trademark Office ("the PTO") for at least the following reasons.

Introduction

The '742 patent teaches the use of an anti-IL6-receptor antibody together with a chemotherapeutic agent to treat multiple myeloma. The PTO position requires that one of ordinary skill in the art would have been motivated to replace the anti-IL-6 receptor antibody of the combination with an anti-VLA-4 antibody. The art was not sufficiently predictable to allow such interchangeability. Although the art, as pointed out by the PTO, recognized the importance of IL-6 in multiple myeloma, it was not predictable to use other combinations, specifically, the combination of an anti-VLA-4 antibody and a chemotherapeutic agent, to treat the disorder. It was not predictable that one could replace the anti-IL-6 antibody with an anti-VLA-4 antibody to address the IL-6 issue. This unpredictability flows from a number of sources. A number of references taught that anti-IL-6 antibodies, by themselves, were ineffective to treat multiple myeloma. The primary reference (*i.e.*, the '742 patent), Bataille *et al.* ("Biological Effects of Anti-Interleukin-6 Murine Monoclonal Antibody in Advanced Multiple Myeloma," *Blood* 86:685-691, 1995) and Van Zaanen *et al.* ("Chimaeric anti-interleukin 6 monoclonal antibodies in the treatment of advanced multiple myeloma: a phase I dose-escalating study," *British Journal of Haematology* 102:783-790, 1998) all show that anti-IL-6 antibodies alone will not work to treat the disorder. Lokhorst *et al.*, the secondary reference relied on by the PTO, concluded from its *in vitro* studies that it was unlikely that VLA-4 is directly involved in signaling processes essential for the regulation of IL-6 production. Thus, it is very difficult to say that this reference suggests interchangeability or that an anti-VLA-4 antibody can be used to solve the IL-6 problem. Finally, the antigenic targets of these antibodies are very different molecules, one being a cytokine and the other an integrin. Thus, although the '742 patent says that anti-IL-6 antibodies and a chemotherapeutic agent can work, that, taken together with the above mentioned teachings of the art, show that it was not at all straightforward or predictable as

to how one would decrease IL-6 with other combinations, and particularly that it was not predictable that an anti-VLA-4 antibody in combination with a chemotherapeutic would do that. This scenario falls far short of the KSR standard relied on by the PTO. That standard requires, as set out in the Office Action, provides that "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." This standard is not met. This is discussed in more detail below.

Discussion

The PTO placed critical reliance on Lokhorst *et al.* to tie anti-VLA-4 Abs to IL-6 reduction in combination with a chemotherapeutic agent to treat the disorder. Lokhorst *et al.* demonstrated at page 2273, second column, and in Fig. 6, that IL-6 secretion by LTBMC adherent cells induced by myeloma cells from three MM patients with active disease and positive for VLA-4 and LFA-1 was inhibited, *in vitro*, by blocking of plasma cell binding using antibodies to VLA-4, CD29, or LFA-1. The PTO concluded that one would use an anti-VLA-4 antibody to treat multiple myeloma, because the antibodies blocked cell-cell contact and inhibited IL-6 secretion. This, however, is not supported by a reading of the reference as a whole, either alone or in combination with other observations in the art. For example, Lokhorst *et al.* state in the conclusion that "Because myeloma tumor cells or plasma cell lines lacking VLA-4, CD44, or LFA-1 are capable of inducing LTBMC IL-6 secretion, it seems unlikely that these adhesion molecules are directly involved in signaling processes essential for the regulation of IL-6 production." Lokhorst *et al.* at page 2276, last sentence of second full paragraph. Thus, the relationship between VLA-4 activity and IL-6 is at best problematic. In view of the art as a whole, this *in vitro* experiment does not suggest that anti-VLA-4 antibodies can be substituted for the anti-IL-6 receptor antibodies described in the '742 patent for treatment of multiple myeloma. The art as a whole demonstrates the unpredictability associated with anti-VLA-4 activity, and indicates that the observations with anti-IL-6 or anti-IL-6 receptor antibodies are not predictive of anti-VLA-4 activity for treatment of multiple myeloma.

Bataille *et al.* describes clinical studies in humans with anti-IL-6 antibodies. In Bataille *et al.*, nine patients with advanced and progressive MM, mainly primary and secondary plasma

cell leukemia, refractory to standard chemotherapy and with a life expectancy less than 1 month, were treated with anti-IL-6 monoclonal antibodies. Bataille *et al.* at page 685, in the paragraph spanning the first and second columns. The authors concluded that "[n]one of the patients treated had improved outcome or achieved remission as defined by standard clinical response criteria for MM." Bataille *et al.* at page 689, second column, second full paragraph (emphasis added). The PTO argued that this reference shows that anti-IL-6 antibodies were effective to treat advanced MM but not acute MM. Applicants do not read Bataille *et al.* as describing two different patient populations and maintains that (i) all the patients in the study were at an advanced stage of multiple myeloma, and (ii) that none of the patients in the study had improved outcome following treatment with an anti-IL-6 antibody. Applicants respectfully request that the PTO point to support for their argument in Bataille *et al.*

Van Zaanen *et al.* describes a phase I clinical trial to investigate toxicity of anti-IL-6 antibodies for treatment of multiple myeloma. By definition, a phase I clinical study only examines toxicity, and not efficacy. Not surprisingly, Van Zaanen *et al.* reported that none of the patients treated achieved a response according to the standard criteria (see the abstract). Van Zaanen *et al.* also reported that the candidate antibody had low toxicity (see the abstract). No conclusions can be drawn from this reference regarding the efficacy of IL-6 to treat MM, and certainly the reference does not indicate that and anti-IL-6 antibody would be effective to treat MM.

The '742 patent reported that anti-IL-6 receptor antibodies were not effective to extend the survival period of mice implanted with human myeloma cells, although anti-IL-6 receptor antibodies in combination with the therapeutic agent melphalan did extend the life span of these mice (see column 20, lines 23-26).

Thus, none of the references discussed in the interviews support the suggestion that anti-IL-6 antibodies would work (alone) for treatment of MM, and further, nothing in the art would lead one of ordinary skill to substitute anti-VLA-4 antibodies for anti-IL-6 antibodies (or anti-IL-6 receptor antibodies) for treatment of MM, even in the presence of a second therapeutic such as a chemotherapeutic agent. See, *e.g.*, the discussion of Lokhorst *et al.* above, wherein Lokhorst *et al.* state that VLA-4 is unlikely to be in the pathway of IL-6 regulation.

One of skill in the art would also not be motivated to substitute an anti-VLA-4 antibody for an anti-IL-6 antibody, because IL-6 and VLA-4 are different types of proteins involved in different biological pathways. IL-6 is a cytokine, which is a protein released by cells that affects the behavior of other cells. As described at column 1 of the '742 patent, IL-6 is a multi-functional cytokine responsible for activation of B-lymphocytes, and which also has been found to influence the function of various other cell types. IL-6 imparts its biological activity through two proteins on the cell membrane. One of the membrane-bound proteins is the IL-6 receptor protein. The IL-6 receptor, in its membrane-bound form, interacts with IL-6, and the receptor-IL-6 complex then binds another membrane-bound protein, gp130. The binding of gp130 to the receptor/IL-6 complex permits the biological activity of IL-6 to be transmitted to the cell. The IL-6 receptor also exists in a soluble form that consists mainly of the extracellular region of the protein. Thus, IL-6, a natural ligand of an IL-6 receptor, is multifunctional and binds to at least two different proteins on the cell surface. In addition, an IL-6 receptor occurs not only on the cell surface but also as a soluble form. These factors alone lead to complexity and unpredictability. For example, one might well expect an antibody to IL-6 receptor to bind the soluble form of the receptor as well as to the membrane bound form. It is not clear from the record if such binding would block binding of endogenous IL-6 to the soluble receptor or what effect that might have on IL-6 mediated cellular processes.

During the telephone conference of October 16, 2008, Applicants' representatives also referenced a textbook definition of IL-6, which states that the two best described actions of the IL-6 cytokine are (1) to cause hepatocytes to synthesize plasma proteins, including fibrinogen, that contribute to the acute phase response, and (2) to serve as a growth factor for activated B cells late in the sequence of B cell differentiation. See Abbas *et al.*, Cellular and Molecular Immunology, 2nd ed. (Philadelphia: W.B. Saunders Company, 1994), 250-251, submitted with the attached Supplemental Information Disclosure Statement. The biology of IL-6 and its natural ligands, one of which is the membrane bound receptor relied on in the PTO arguments, is far more complex and unpredictable than is allowed for by the PTO arguments.

Very much unlike IL-6, VLA-4 is an integrin molecule, which is membrane bound, and involved in mediating cell-cell and cell-extracellular matrix contacts. VLA-4 is expressed on cells involved in the immune response, often in response to trauma or tissue damage, and VLA-4

has also been found to be expressed on some types of multiple myeloma cells. See, *e.g.*, the Specification at page 6, lines 2-4, and Lokhorst *et al.* at page 2276, last sentence of the second full paragraph. Thus, the role of VLA-4 alone in multiple myeloma is complex and poorly understood, as the role of IL-6 is also complex and poorly understood. The nature of the fields of study surrounding each molecule alone is complex, and the overlap in these fields of study is even more complex. There is no teaching in the art that would lead one of ordinary skill to conclude that one of these molecules could be substituted for the other for any purpose whatsoever, let alone for the treatment of multiple myeloma.

The teachings of the art can be summarized as follows. The art shows that anti-IL-6 antibodies (or anti-IL-6 receptor antibodies) cannot function alone to treat multiple myeloma. Lokhorst *et al.* teaches that VLA-4 is unlikely to be in the pathway of IL-6 regulation. The art also indicates that the IL-6 and VLA-4 signaling pathways are discreet and the ways that these pathways interact, if at all, is not clear. Therefore, even though a combination of anti-IL-6 receptor antibody and melphalan extended the lifespan of a mouse model of MM (see the '742 patent), the art, when taken as a whole, shows that it was not at all predictable as to how one would decrease Il-6, and particularly it was not predictable that an anti-VLA-4 antibody in combination with a chemotherapeutic would do that.

The PTO quoted KSR International Co. v. Teleflex Inc., 127 S. Ct. 1727 (2007), as stating "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." See Office Action mailed January 30, 2008, at page 7. The PTO's reliance on KSR is misplaced. The PTO's argument takes obviousness analysis well outside the bounds of the case law and, in particular, far beyond the limits set in KSR.

The facts in KSR involved a small number of simple elements, combined in a straight-forward way, in the context of a highly predictable technology. The decision in KSR criticized the court below for rigid application of the teaching, suggestion, or motivation test (the TSM test) and for reliance on the proposition "that a patent claim cannot be proved obvious by merely showing that the combination of elements was "obvious to try." The Supreme Court allowed

that, under certain carefully delineated circumstances, "obvious to try" might be an acceptable test, and indeed found it an acceptable test for the fact pattern before it. The KSR Court was very careful, however, to qualify its language and limit its holding to distinguish the simple predictable fact pattern based on the combination of a few identified, known simple elements in a predictable art to meet a known problem found in KSR from more complex and unpredictable fact patterns, such as the one in the instant matter. The language of the holding in KSR is instructive:

> The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try." When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp.

KSR at 1742 (emphasis added, citations omitted).

The facts in the instant matter do not present a finite number of identified, predictable solutions. Evidence presented by the Applicants show the field was complex and that the effects of the relevant antibodies were unpredictable. The art cannot be properly interpreted to say that an anti-IL-6 antibody can predictably replace an anti-VLA-4 antibody. As evidenced by this and previous submissions, the pathways are too complex, the receptors and ligands involved affect too many different cells and pathways, and the references are open to too many interpretations to allow one to say that an anti-IL-6 antibody can predictably replace an anti-VLA-4 antibody. The fact pattern of the instant matter bears no resemblance to the fact patterns characterized by "a finite number of identified, predictable solutions," and found by the KSR Court to be appropriate for "obvious to try analysis." In short, the claims are unobvious under KSR.

KSR was careful to limit the analytical framework for determining obvious in unpredictable areas. In a more recent case, Eisai Co. Ltd. And Eisai, Inc., v. Dr. Reddy's Laboratories Ltd and Dr. Reddy's Laboratories, Inc., and Teva pharmaceuticals USA Inc., 2007-1397, -1398, (Fed. Cir. 2008) the Federal Circuit applied the holding of KSR. The Federal Circuit expressly acknowledged the sharp limitations the Supreme Court placed on the analysis

when applied in the unpredictable arts. The holding in Eisai compels a finding of non-obviousness in the instant matter. The Eisai court provided the following analytical framework:

> The Supreme Court's analysis in KSR thus relies on several assumptions about the prior art landscape. First, KSR assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might identify a problem and pursue potential solutions. Second, KSR presupposes that the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound. See Takeda Chem. Indus. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1356 (Fed. Cir. 2007). ("Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound."). Third, the Supreme Court's analysis in *KSR* presumes that the record before the time of invention would supply some reasons for narrowing the prior art universe to a "finite number of identified, predictable solutions," 127 S. Ct. at 1742. In Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc., 520 F.3d 1358, 1364 (Fed. Cir. 2008), this court further explained that this "easily traversed, small and finite number of alternatives . . . might support an inference of obviousness." To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.
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> Emphasis added.

This analysis requires at least three elements. Even if the art provided the first required element, a starting point, namely the use of an anti-IL-6 receptor antibody, it fails utterly to provide the second element. Application of KSR, as interpreted in Eisai, includes the following element, "Second, KSR presupposes that the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound." That element is entirely lacking—as discussed above the art provides no reason to believe an anti-VLA-4 antibody could be used in the place of an anti-IL-6 receptor antibodies. There is reason to make a particular modification to achieve the claimed compound. The art also fails to provide the third element. The art does not supply the required assembly of a "finite number of identified, predictable solutions."

Clearly, the "solutions" provided by the art fall short of being "genuinely predictable" as mandated in Eisai. The PTO arguments fail to pass the "difficult hurdle" recognized by the Eisai court and presented by the complex and unpredictable technology at issue here.

In view of the foregoing remarks, which summarize the statements made in the recent interviews with the Examiners and Applicants' representatives, Applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 USC § 103.

CONCLUSION

In view of the foregoing, Applicants contend that the present claims are in condition for allowance, and notice to this effect is respectfully requested. Should the Examiner maintain any of the present grounds for rejection, the favor of a telephone call to the undersigned is respectfully requested.

No fees are believed to be due. However, any necessary charges, or any credits, should be applied to Deposit Account No. 06-1050, referencing Attorney Docket No. B2047-700731.

Respectfully submitted,
Mundy *et al., Applicants*

By: /Allyson R. Hatton/

Allyson R. Hatton, Ph.D., Reg. No. 54,154
LOWRIE, LANDO & ANASTASI, LLP
One Main Street
Cambridge, Massachusetts 02142
United States of America
Telephone: 617-395-7000
Facsimile: 617-395-7070

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